

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 02/056800 A2

- (51) International Patent Classification⁷: **A61F 2/08**
- (21) International Application Number: PCT/US01/47644
- (22) International Filing Date: 7 December 2001 (07.12.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/254,378 8 December 2000 (08.12.2000) US
- (71) Applicant (for all designated States except US): **OS-TEOTECH, INC.** [US/US]; 51 James Way, Eatontown, NJ 07724 (US).
- (71) Applicants and
- (72) Inventors: **BOYCE, Todd, M.** [US/US]; 515 Wellington Place, Aberdeen, NJ 07747 (US). **SHIMP, Lawrence, A.** [US/US]; 313 Route 79, Morganville, NJ 07751 (US).
- (74) Agents: **DILWORTH, Peter, G.** et al.; Dilworth & Barrese, LLP, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/056800 A2

(54) Title: IMPLANT FOR ORTHOPEDIC APPLICATIONS

(57) Abstract: An implant for orthopedic applications includes a quantity of flexible, elongated elements at least some of which possess connective tissue-healing activity, the elongated elements being arranged in substantially common alignment along their longitudinal axis.

IMPLANT FOR ORTHOPEDIC APPLICATIONS

BACKGROUND OF THE INVENTION1. Field of the Invention

The present invention relates to an implant which is useful for a variety of orthopedic applications. More particularly, the present invention relates to an implant
5 useful for treating bone injuries, defects, etc., such as spinal disorders for which spinal fusion is indicated and the repair or replacement of ligaments, tendons and/or cartilage.

2. Description of Related Art

A variety of implants having application as artificial bone, ligaments, tendons,
10 cartilage, and the like, are known. U.S. Patent No. 4,089,071 describes a material for making bone endoprostheses featuring a laminated structure of net-like construction. U.S. Patent No. 5,092,887 describes an elongated artificial ligament made from demineralized bone which is said to exhibit compliant elasticity and high longitudinal strength. U.S. Patent No. 5,263,984 describes a prosthetic ligament made up of a
15 quantity of substantially aligned, elongated filaments each of which is a biocompatible, resorbable fibril made, e.g., of collagen, elastin, reticulin, cellulose, algenic acid or chitosan. U.S. Patent No. 5,711,960 describes an implant, useful *inter alia*, as a prosthetic or filling for a defective bone, which utilizes, as a base material, a biocompatible bulk structure of a three-dimensionally woven or knitted fabric of
20 organic fibers whose surfaces have been biologically activated or inactivated. U.S. Patent No. 6,090,998 describes a bone implant, useful for the repair or replacement of

ligaments, tendons and joints, which includes at least one mineralized segment and at least one demineralized, flexible segment.

Developing cells are known to migrate along surfaces. When the surface is oriented, the potential exists to somewhat control the direction of growth. It has been
5 observed by the inventors in animal studies that fibrous materials provide better osteoconduction than particle based materials. Therefore, a material which guides the formation of new tissue would have the ability to direct osteoconduction as well as other types of tissue growth. Such a material, by directing the formation of new tissue, would be expected to demonstrate improved strengthening effects. In addition,
10 a fibrous implant, unlike particle-based implants, would tend to remain where placed in the body and would resist being dislodged therefrom.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an implant which is useful for the treatment of defects and injuries of bone, ligaments, tendons and cartilage.

15 It is a further object of the invention to provide an implant that is biocompatible and will not be rejected by the host.

It is still a further object of the invention to provide an implant for various orthopedic applications which can be combined with one or more separate therapeutically useful substances or structurally useful biomaterials, e.g., titanium
20 wire or mesh.

By way of attaining these and other objects of the invention, an implant is provided which comprises a quantity of flexible, elongated elements at least some of which possess connective tissue-healing activity, the elements being arranged in substantially common alignment along their longitudinal axis.

Significant advantages of the implant flow from the substantial alignment of the elongated members along their longitudinal, or major, axis. Thus, when the elongated members are thus aligned to provide, e.g., a woven or braided structure, the result is an implant which is generally stronger than the elongated members from which the implant is made. In addition, the implant can be made to possess dimensions which could not be achieved with naturally occurring implant materials such as whole bone sections.

Still another advantage resides in the ability of a particular implant to utilize combinations of different materials as sources for its elongated members. Selection from among a large variety of such materials expands the range of biological and/or mechanical properties that can be built into a given implant.

The implant of the present invention, unlike conventional metallic implants, will not stress shield the bone at the implant site. Therefore, any tendency for already existing healthy bone to be resorbed at the implant site will be reduced. In addition, unlike metallic implants, the implant of this invention will not interfere with the use of postoperative plain film X-rays, MRI or CT scans.

The expression "elongated elements" refers to the structural units constituting the implant of this invention and having the appearance of filaments, threads, strips and similarly elongated configurations. The elongated elements can be separate units for their entire length or two or more of the elements can have a common point of attachment, e.g., as shown in the implant of Fig. 1a.

The term "biocompatible" and expressions of like import shall be understood to mean the absence of unacceptable detrimental biological response, e.g., stimulation of a severe, long-lived or escalating biological response to an implant and is distinguished from a mild, transient inflammation which accompanies implantation of

essentially all foreign objects into a living organism and is also associated with the normal healing response. Thus, materials which alone in appropriate quantities are generally considered nonbiocompatible can be considered biocompatible within the aforesaid meaning if present in small enough quantities such that they do not elicit a
5 significant level of undesirable or detrimental tissue response.

The expression "connective tissue-healing activity" refers to the ability of the implant of the invention to participate in the repair, regeneration, healing, etc., of connective tissue, e.g., bone, ligament, tendon or cartilage, by one or more mechanisms including chondrogenesis, osteoinduction, osteogenesis and
10 osteoconduction.

The term "chondrogenic" as used herein shall be understood to refer to the ability of a material or substance to induce or otherwise participate in the formation of cartilage.

The term "osteoinductive" as used herein shall be understood to refer to the
15 ability of a material or substance to recruit cells from the host which have osteogenic potential and the ability to form ectopic bone.

The term "osteogenic" as used herein shall be understood to refer to the ability of a material or substance to induce new bone formation via the participation of living cells from within the substance.

20 The term "osteoconductive" as used herein shall be understood to refer to the ability of a material or substance or material to provide surfaces that are receptive to the growth of new host bone.

The expression "substantially common alignment" refers to the relative orientation of the elongated elements constituting the implant and includes woven,

knitted, braided, or twisted arrangements of individual elements as well as subassemblies of several elongated elements formed into yarns, twines, strands, etc.

The term "resorbable" refers to the ability of materials to be broken down by normal biochemical and/or physical processes such as erosion, dissolution, etc.

5 The term "remodeling" refers to the process whereby materials are broken down and then replaced by host tissue, e.g., by resorption of existing bone tissue by osteoclasts and formation of new bone tissue by osteoblasts.

Other advantages of the present invention will become apparent to one skilled in the art from the following written description and accompanying figures.

10 BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-1E are diagrammatic representations of implants in accordance with the present invention. In FIG. 1A, an elongated section of bone is cut or machined to provide three relatively wide elongated elements arranged in a braided pattern. In FIG. 1B, the elongated section of bone is cut or machined to provide elongated
15 elements which are formed into yarns with the yarns subsequently being formed into braids. FIGS. 1C-1E schematically depict demineralized bone strips arranged into various other structures.

DETAILED DESCRIPTION OF THE INVENTION

The implant of this invention is fabricated in whole or in part from flexible
20 elongated elements, advantageously biocompatible in character, e.g., connective type tissues obtained from human and animal tissues and natural and synthetic fibers including, but not limited to, demineralized bone, tendon, ligament, collagen, elastin, reticulin, cellulose, alginic acid, chitosan, small intestine submucosa, silk, nonresorbable and resorbable synthetic polymeric fibers, and the like. The elongated
25 elements can also be obtained from microorganisms, particularly genetically

engineered microorganisms such as yeast and bacteria and genetically engineered eucaryotic cell cultures such as Chinese hamster ovary cell lines, HeLa cells, etc. For example, U.S. Patent Nos. 5,243,038 and 5,989,894, each of which is incorporated herein by reference, describes the expression of spider silk protein, collagen proteins, 5 keratins, etc., using genetically engineered microorganisms and eucaryotic cell lines.

When the elongated elements are fabricated in whole or in part from tissues such as bone, tendon, ligament, small intestine submucosa tissue, and the like, such tissues are first processed to remove any blood and debris that may be associated therewith and the tissues are then sterilized employing routine procedures such as 10 those described below. The processed tissues are then fashioned into elongated elements whose dimensions are selected so that when assembled into the implant, the latter will have sufficient length to span, and be affixed to, the implant site, and sufficient width and thickness to impart such desirable properties as toughness, flexibility and strength to the implant.

15 The elongated tissue elements can be formed into implants having a variety of configurations such as those shown in FIGS. 1A-1E. For example, FIG. 1A schematically depicts one embodiment in which a sheet of bone is further cut or machined into three elongated elements of about the same width which are then formed into a braid. FIGS. 1B-1E schematically depict other embodiments wherein a 20 section of bone is cut or machined to provide a quantity of elongated elements which are then assembled into the implants shown.

The overall dimensions of the flexible elongated elements making up the implant of this invention can vary widely depending on the dimensions of the site to which the implant is to be affixed. Typically, these dimensions will range from about 25 1 cm to about 1 meter in length, preferably from about 3 cm to about 8 cm in length,

from about 0.5 mm to about 30 mm in thickness, preferably from about 2 mm to about 10 mm in thickness, and from about .05 mm to about 150 mm in width, preferably from about 2 mm to about 10 mm in width.

While fully mineralized bone, tendon, ligament, small intestine submucosa, collagen tissues, etc., in themselves are not particularly osteoinductive, such tissues can be rendered osteoinductive by subjecting the tissue to various procedures and/or incorporating one or more osteoinductive substances in the tissues. For example, the mineral content of bone tissue can be reduced by demineralization, a process which results in the removal of the inorganic components of the bone, largely hydroxyapatite, which gives bone its characteristic rigidity and structural properties. The resultant demineralized bone is both flexible and osteoinductive. Bone, tendon, ligament, small intestine submucosa and collagen tissues can be rendered osteoinductive by association with, or incorporation of, various osteoinductive materials which include, but are not limited to, growth factors such as bone-derived growth factor, bone morphogenic proteins, osteogenic proteins such as OP-1, hormones, growth hormone, platelet derived growth factor (PDGF), insulin-like growth factors (IGF-1)(IGF-2), DNA-encoding various therapeutic agents such as growth factors and hormones, gene activated matrix, i.e., a matrix containing DNA encoding therapeutic proteins utilized to promote cell growth, which in turn, promote DNA transfer into repair cells, demineralized bone in the form of particles, powder, gel, liquid, etc, ceramic powders of calcium phosphate and/or apatite (hydroxyapatite) and bioglasses. Bone morphogenic proteins can be obtained from Genetics Institute, Inc. (Cambridge, MA) and Stryker Corporation (Kalamazoo, MI) and may also be prepared by one skilled in the art as described, e.g., in U.S. Patent Nos., 5,187,076, 5,366,875, 4,877,864, 5,108,922, 5,116,738, 5,013,649, 5,106,748, WO93/00432,

WO94/26893 and WO94/26892, each of which is incorporated by reference herein.

All osteoinductive factors are contemplated whether they are obtained as above or isolated from bone or other human or animal tissues. Methods for isolating bone morphogenic protein from bone are described, e.g., in U.S. Patent No. 4,294,753, incorporated herein by reference. Methods of preparing demineralized bone powder, demineralized bone particles, and demineralized bone in the form of a liquid, and demineralized bone in the form of a gel are well known in the art as described, e.g., in U.S. Patent Nos. 5,314,476, 5,507,813, 5,073,373, and 5,405,390, respectively, each of which is incorporated by reference herein. Methods of preparing osteogenic proteins, such as OP-1 are described, e.g., in U.S. Patent No. 6,048,964 which is incorporated by reference herein. Methods of transferring DNA-encoding therapeutic proteins into repair cells utilizing gene activated matrix are described, e.g., in U.S. Patent No. 5,962,427 which is incorporated by reference herein. Methods of preparing ceramic powders of calcium phosphate and/or hydroxyapatite are described, e.g., in U.S. Patent No. 4,202,055 and 4,713,076, each of which is incorporated by reference herein. Methods of preparing bioglasses are described, e.g., in WO 98/44965, which is incorporated by reference herein. Suitable methods of incorporation or association of such osteogenic factors include coating, immersion saturation, packing, spraying, e.g., plasma spraying, injecting into the bone tissue, etc.

When desirable, e.g., for preparing an implant suitable for soft tissue repair, the flexible elongated elements constituting the implant can be treated to so as to reduce their osteoinductive properties. For example, demineralized bone is known to possess osteoinductive characteristics. When desirable, such characteristics can be reduced or eliminated by appropriate further treatment. For example, the osteoinductive proteins in the demineralized bone can be denatured, and thus

deactivated, by reaction with, for example, a chemical denaturant such as glutaraldehyde or formaldehyde. Demineralized bone treated in this way is known to support the formation of fibrous tissue and as such, exhibits connective tissue-healing activity although, of course, through a mechanism other than that of osteoinduction.

- 5 The degree of denaturation can be controlled to give the desired physical and biological properties. Other denaturation methods include irradiation and thermal treatment. Alternatively, osteoinductive proteins can be extracted from the demineralized bone employing extractants such as guanidine hydrochloride.

- Implants of this invention containing bone or other tissue material can be
10 further treated by tanning or other means known in the art to reduce their antigenicity. For example, glutaraldehyde treatment (see U.S. Patent No. 5,053,049 which is incorporated by reference herein) can be used for this purpose.

- Employing a milling technique, elongated bone elements ranging in median length from about 2 up to about 200 mm or more (as in the case of the long bones); in
15 median thickness from about 0.05 to about 2mm and in median width from about 1 to about 20 mm can be readily obtained. Another procedure for obtaining the elongated bone particles herein, particularly useful for elements of bone of up to about 100 mm in length, is the bone milling apparatus described in U.S. Patent No. 5,607,269 the contents of which are incorporated by reference herein. Use of this apparatus results
20 in the production of long, thin bone strips which tend to curl lengthwise into tube-like structures.

- Depending on the procedure employed for producing the elongate bone elements, one can obtain a mass of bone elements containing at least about 60 weight percent, preferably at least about 70 weight percent, and most preferably at least about
25 80 weight percent of bone elements possessing a median length of from about 2 to

about 200 mm or more and preferably from about 10 to about 100 mm, a median thickness of from about 0.05 to about 2 mm and preferably from about 0.2 to about 1 mm and a median width of from about 1 mm to about 20 mm and preferably from about 2 to about 5 mm. These bone elements can possess a median length to median thickness ratio of at least about 50:1 up to about 500:1 or more and preferably from about 50:1 to about 100:1 and a median length to median width ratio of from about 10:1 to about 200:1 and preferably from about 50:1 to about 100:1.

If desired, the mass of elongated bone elements can be graded into different sizes to reduce or eliminate any less desirable size(s) of elements which may be present. In overall appearance, the elongated bone elements can be described as filaments, fibers, threads, slender or narrow strips, etc. As already noted and depending on the manner in which they are produced, these elongated elements may have a tendency to curl lengthwise into tube-like structures.

When the implant of this invention is fabricated from bone, the bone is preferably chosen from a cortical bone such as the femur, tibia, fibula, radius or ulna. The bone elements can be obtained from cortical, cancellous and/or corticocancellous bone which can be of autogenous, allogenic and/or xenogeneic origin. Porcine bone is a particularly advantageous type of xenogeneic bone tissue which can be used as a source for the elongated bone elements of this invention.

Following the shaving, milling or other technique whereby they are obtained, the elongated bone elements are subjected to demineralization in order to reduce their inorganic content and, as may be necessary for a particular embodiment, to increase their flexibility. Demineralization of the bone elements will ordinarily result in elongated elements of slightly smaller dimensions than those of the mineralized elements from which they were obtained.

The elongated bone elements can be demineralized in accordance with known and conventional procedures. The mineral content of bone can be removed to varying degrees. The term "fully demineralized" as it applies to an elongated bone element refers to a bone element possessing less than about 8, preferably less than about 1, 5 weight percent of its original inorganic mineral content. The term "partially demineralized" as it applies to an elongated bone element means that the bone element possesses from about 8 to about 90 weight percent of its original inorganic mineral content. The term "superficially demineralized" as it applies to an elongated bone element refers to a bone element possessing at least 90 weight percent of its 10 original inorganic mineral content. The term "demineralized" as it applies to an elongated bone element includes any one or combination of the foregoing types of demineralized elongated bone elements. The use of superficially, partially or fully demineralized bone can, in some embodiments, be particularly advantageous since demineralized bone exhibits considerably greater initial osteoinductive activity than 15 fully mineralized bone.

Demineralization can precede or follow the cutting, slicing, milling, etc., of the bone into elongated elements. Thus, a whole section of bone, e.g., a diaphyseal shaft, can first be demineralized to the extent desired after which it is machined to provide the individual elongated bone elements. Alternatively, the whole bone can be 20 subdivided into individual elongated bone elements which are thereafter demineralized to the desired level.

Of course it will be understood by those skilled in the art that the bone elements will be demineralized to such an extent that they can be worked to form the implant of the invention herein. Therefore, when the bone elements are of such size 25 as to be relatively inflexible prior to demineralization, they can be demineralized to

the point where they are flexible and capable of being worked, e.g., woven, braided, spun, etc. When bone elements are of such dimensions that they are relatively flexible prior to demineralization, a lesser degree of demineralization may be appropriate. The extent of demineralization necessary to obtain a bone element that is

5 workable can be readily determined by one skilled in the art employing routine experimentation.

Demineralization of the elongated bone elements can be conducted using conventional procedures that are well known in the art, e.g., subjecting the bone section to strong acids such as hydrochloric acid as described, e.g., in Reddi et al.,

10 *Proc. Nat. Acad. Sci.* 69:1601-5 (1972), incorporated herein by reference. The extent of demineralization is a function of the strength of the acid solution, the shape of the bone and the duration of the demineralization treatment. Reference in this regard may be made to Lewandrowski et al., *J. Biomed. Materials Res.* 31:365-372 (1996), incorporated herein by reference.

15 In a preferred demineralization procedure, the elongate bone elements are subjected to a defatting/disinfecting step which is followed by an acid demineralization step. A preferred defatting/disinfectant solution is an aqueous solution of ethanol, the ethanol being a good solvent for lipids and the water being a good hydrophilic carrier to enable the solution to penetrate more deeply into the bone

20 particles. The aqueous ethanol solution also disinfects the bone by killing vegetative microorganisms and viruses. The preferred concentration range of the defatting solution is from about 60 to about 85 weight percent alcohol and most preferably about 70 weight percent alcohol. Following defatting, the bone elements are immersed in acid over time to effect their demineralization. Acids which can be

25 employed in this step include inorganic acids such as hydrochloric acid and organic

acids such as peracetic acid. Generally, the concentration of inorganic acid utilized to achieve demineralization is from about 0.1N to about 2N and more preferably from about 0.2 N to about 1.0 N. The time of exposure to the acid is increased for lower acid concentrations and decreased for the higher acid concentrations. After acid
5 treatment, the demineralized bone elements are rinsed with sterile water for injection to remove residual amounts of acid and thereby raise the pH.

The wet demineralized bone elements can then be immediately formed into the implant of this invention in accordance using methods well known in the art, e.g., those described in U.S. Pat. No. 5,263,984 the contents of which are incorporated by
10 reference herein, or stored under aseptic conditions, advantageously in a lyophilized state, for processing at a later time.

When the bone elements are shorter than the desired length of the implant, they can be combined with fibers and/or other materials such that a final implant of the desired length is produced. For example, the relatively short bone elements can be
15 combined with other materials in a known manner, e.g., to form a spun yarn, which can then be woven to form the implant of the invention. Thus, the short bone elements can be combined with demineralized bone elements of greater length or with bioresorbable polymeric fibers, ceramic or glass fibers, or biocompatible metal fibers of suitable length to produce a composite yarn which can then be woven using
20 standard techniques to produce the implant of the invention.

Optionally, the short bone elements can be combined with bioresorbable thermoplastic material that is formed into spun-bonded and/or non-woven fabrics. For example, after the bioresorbable thermoplastic material has been formed into a first web, the short bone elements can be applied to the first web and then sandwiched
25 with a second web to form a controlled elastic composite material. The methods of

forming a composite material disclosed in U.S. Patent Nos. 6,124,001 and 6,132,871 are incorporated by reference herein and are suitable for forming the aforescribed elastic composite.

In one embodiment, the bone comprises a plurality of elongated bone
5 elements. Typically, the bone is obtained from a suitable vertebrate and processed by conventional techniques to remove blood and lipid from the bone. The bone can then be cut into elongated sections by techniques which are well known in the art, e.g., longitudinally cutting an entire bone section or relatively large portion of bone into elongated sections using a band saw or a diamond-bladed saw, or milling the surface
10 of an entire bone or relatively large portion of bone. Alternatively, the bone can be cut by making transverse cuts to prepare a bone section of the appropriate length, followed by longitudinal cuts using a band saw or a diamond cut saw. As stated above, elongated elements of bone can be further cut or machined into a variety of different shapes. In overall appearance the elongated bone elements can be described
15 as narrow or thick strips, segments, sheets, rods, struts, etc. The elongated elements can be further processed to remove residual blood and lipid residue.

Prior or subsequent to cutting or milling of the bone into elongated elements, the bone is preferably demineralized to reduce its inorganic content utilizing the defatting/demineralization procedure described herein above. After acid treatment,
20 the elongated bone elements are rinsed with sterile water for injection, buffered with a buffering agent to a final predetermined pH and then finally rinsed with water for injection to remove residual amounts of acid and buffering agent or washed with water to remove residual acid and thereby raise the pH.

In a particularly useful embodiment, the elongated bone elements can be segmentally demineralized employing procedures known in the art as described, e.g., in U.S. Patent No. 6,090,998, which is incorporated herein by reference.

Alternatively, the end portions of the elongated bone elements can be surface
5 demineralized by any convenient method. For example, the bone elements can be subjected to demineralization conditions for a period of time sufficient to demineralize only their surfaces.

In an alternative embodiment, demineralized bone sections (approximately 6 bone sections) are combined longitudinally into three small bundles, each having from
10 about 1 to about 3 bone sections. The three bundles are then braided. Various methods of braiding and types of braids any of which may be useful in producing the material of the invention herein are also described, e.g., by Shaw, *KNOTS - Useful & Ornamental*, Bonanza Books, New York (1983), incorporated herein by reference. The ends of the braided demineralized bone section can then be glued together using a
15 fixation agent to prevent their unraveling or they can be held together with a biocompatible polymer or metal band.

In another embodiment, demineralized bone strips can be cut from sheets composed of elongated bone particles, commercially available as GRAFTON® Flex (Osteotech, Eatontown, NJ) as described, e.g., in U.S. Patent No. 5,507,813, the
20 contents of which are incorporated by reference herein.

To increase the mechanical strength of bone strips fabricated from bone, chemical linkages can be formed between adjacent bone elements employing, e.g., any of the procedures for accomplishing this disclosed in U.S. Patent No. 6,123,731, the contents of which are incorporated herein by reference.

Medically/surgically useful substances which promote or accelerate healing can be incorporated in the implant of this invention. Useful substances of this kind which can be incorporated into the implant include, e.g., collagen, insoluble collagen derivatives, etc., and soluble solids and/or liquids dissolved therein, e.g., antiviral agents, particularly those effective against HIV and hepatitis; antimicrobials and/or antibiotics such as erythromycin, bacitracin, neomycin, penicillin, polymyxin B, tetracyclines, viomycin, chloromycetin and streptomycins, cefazolin, ampicillin, azactam, tobramycin, clindamycin, and gentamicin, etc.; biocidal/biostatic sugars such as dextran, glucose, etc.; amino acids; peptides; vitamins; inorganic elements; co-factors for protein synthesis; hormones; endocrine tissue or tissue fragments, synthesizers; enzymes such as collagenase, peptidases, oxidases, etc.; polymer cell scaffolds with parenchymal cells; angiogenic drugs and polymeric carriers containing such drugs; collagen lattices; antigenic agents; cytoskeletal agents; cartilage fragments, living cells such as chondrocytes, bone marrow cells, mesenchymal stem cells; natural extracts; genetically engineered living cells or otherwise modified living cells; tissue transplants; demineralized bone powder (or "demineralized bone matrix" as it may also be referred to); DNA delivered by plasmid or viral vectors; autogenous tissues such as blood, serum, soft tissue, bone marrow, etc.; bioadhesives; bone morphogenic proteins; osteoinductive factor; fibronectin; transforming growth factor-beta; endothelial cell growth factor; cementum attachment extracts; ketaserin; insulin-like growth factor; platelet derived growth factors; epidermal growth factor; interleukin; human alphathrombin; fibroblast growth factors; periodontal ligament chemotactic factor; human growth hormone; animal growth hormone; growth hormones such as somatotropin; bone digesters; antitumor agents; immunosuppressants; permeation enhancers, e.g., fatty acid ester such as laureate, myristate

and stearate monoesters of polyethylene glycol, enamine derivatives, alpha-keto aldehydes, etc.; and, nucleic acids. Preferred biomedically/ surgically useful substances are bone morphogenic proteins and DNA delivered by plasmid or viral vector. Suitable methods of incorporation include coating, immersion saturation, 5 packing, co-lyophilization wherein the substance is placed on the bone graft and lyophilized, spraying, injecting, etc. The amounts of medically/ surgically useful substances utilized can vary widely with optimum levels being readily determined in a specific case by routine experimentation.

The implant herein can also be fabricated in whole or in part from tendon, 10 ligament and/or small intestine submucosa tissues. These tissues are not osteoinductive but can be made so by incorporating various osteoinductive materials as described above. Tendon tissue useful for fabricating the material includes, but is not limited to, fascia lata, semitendinosus, achilles tendon and patella tendon tissue. Ligament tissue can consist of an entire excised ligament or elongated section thereof. 15 Small intestine submucosa tissue can be obtained and processed as described in U.S. Patent No. 4,902,508, the contents of which are incorporated by reference herein. The tendon, ligament and small intestine submucosa tissues can be obtained from autogeneic, allogeneic or xenogeneic sources and preferably are obtained from an autogeneic or allogeneic source. The tissues can be excised and cut into a plurality of 20 elongated elements employing methods known in the art. Reduction of the antigenicity of allogeneic and xenogeneic tissue can be achieved by treating the tissues with various chemical agents, e.g., extraction agents such as monoglycerides, diglycerides, triglycerides, dimethyl formamide, etc., as described, e.g., in U.S. Patent No. 5,507,810, the contents of which are incorporated by reference herein. 25 Medically/surgically useful substances as described above can also be incorporated in

or associated with the tendon, ligament and small intestine submucosa tissue as described above with respect to elongated elements obtained from bone.

The implant can also be fabricated from collagen tissue which can be obtained from any autogeneic, allogeneic or xenogeneic source, preferably from an autogeneic or allogeneic source. Collageneous tissue sources include, but are not limited to, skin, tendon, intestine and dura mater obtained from animals, transgenic animals and humans. Collageneous tissue can also be obtained by genetically engineering microorganisms to express collagen as described, e.g., in aforementioned U.S. Patent No. 5,243,038. Procedures for obtaining and purifying collagen are well known in the art and typically involve acid or enzyme extraction as described, e.g., in U.S. Patent No. 5,263,984, the contents of which are incorporated by reference herein. Collagen is also commercially available (Pentaparm). The purified collagen is then subjected to further processing to obtain collagen fibers or collagen threads, which can optionally be treated with crosslinking agents, e.g., glutaraldehyde, to improve their strength and/or with various medically/surgically useful substances as described above. The collagen threads can be arranged to form various structures, such as a woven or non-woven fabric, bundle or braid, etc. by various techniques known in the art as described, e.g., in U.S. Patent Nos. 5,171,273 and 5,378,469, each incorporated herein by reference, to provide the implant of the invention. For example, U.S. Patent No. 5,171,273 describes the preparation of high-strength collagen fibers by dissolving Type I collagen in dilute hydrochloric acid, extruding the solution into a specific fiber formation buffer to reconstitute the collagen fibers. The reconstituted collagen fibers are subsequently crosslinked with glutaraldehyde or other chemical agents and treatments. The fibers are then processed into woven or non-woven materials.

U.S. Patent No. 5,378,469 describes methods for the production of high strength collagen threads wherein collagen is extruded into a dehydrating agent, e.g., polyethylene glycol, which has a higher osmotic pressure than that of the collagen solution and a pH from about 5 to 10 which results in the formation of collagen
5 threads. If desired, the collagen threads can be crosslinked using various chemical agents. The collagen threads are then utilized to form braided constructs, plied into yarn, and knitted to provide the implant of this invention.

Various constructs of the elongate elements, fibers and threads can be formed utilizing well known techniques, e.g., braiding, plying, knitting, weaving, that are
10 applied to processing natural fibers, e.g., cotton, silk, etc., and synthetic fibers made from synthetic bioabsorbable polymers, e.g., poly(glycolide) and poly(lactic acid), nylon, cellulose acetate, etc.. See, e.g., Mohamed, *American Scientist*, 78: 530-541 (1990). For example, aforementioned U.S. Patent No. 5,378,469 describes the braiding of crosslinked and noncrosslinked collagen threads using a harness braiding
15 machine (New England Butt Co., Providence, RI). Specifically, collagen thread is wound onto cylindrical stainless steel spools. The spools are then mounted onto the braiding carousel, and the collagen thread is then assembled in accordance with the instructions provided with the braiding machine. In one particular run, a braid was formed of four collagen threads, which consisted of two threads of uncrosslinked
20 collagen and two threads of crosslinked collagen.

The elongate particles, fibers, and threads can also be plied into yarns using the same methods and same machinery known to those skilled in the art in plying threads made out of other material, e.g., cotton, polyester, etc. For example, aforementioned U.S. Patent No. 5,378,469 describes the production of a 60 ply yarn
25 from noncrosslinked collagen threads. Therein, 4 collagen threads were twisted

together. Three of the resultant 4-ply strands were then twisted together in the opposite direction, and then 5 of the resultant 12 ply strands were twisted in the opposite direction.

The elongated elements and/or fibers and/or threads and/or braided threads or
5 plied yarns can then be knitted into tubular or flat fabrics by using techniques known to those skilled in the art of producing fabrics manufactured from other types of threads. Various medically/surgically useful substances as described above can be incorporated in, or associated with, the braided, knitted, or woven materials.

The implant can also be fabricated in whole or in part from a synthetic
10 biocompatible bioabsorbable polymer or copolymer, a synthetic biocompatible non-bioabsorbable polymer or copolymer, and combinations thereof. As used herein, "bioabsorbable polymer" refers to a polymer or copolymer which is absorbed by the body. "Non-bioabsorbable polymer" refers to a polymer or copolymer which remain in the body without substantial bioerosion. Examples of synthetic biocompatible
15 bioabsorbable polymers or copolymers include, but are not limited to, poly(lactide), poly(glycolide), poly(epsilon-caprolactone), poly(p-dioxanone), poly(epsilon-caprolactone-co-p-dioxanone) and poly(lactide-co-glycolide) as described, e.g., in U.S. Patent Nos. 5,705,181 and 5,393,594, each incorporated herein by reference; bioabsorbable block copolymers made of hard phase forming monomers, e.g.,
20 glycolide and lactide, and soft phase monomers, e.g., 1,4 dioxane-2-one and caprolactone, as described, e.g., in U.S. Patent No. 5,522,841, incorporated herein by reference; and natural materials such as cotton, and catgut. Examples of synthetic biocompatible non-bioabsorbable polymers include, but are not limited to, homopolymers and copolymers of polypropylene, polyamides, polyvinylchlorides,
25 polysulfones, polyurethanes, polytetrafluoroethylene, etc. The biocompatible material

fabricated from the biocompatible polymer can have incorporated within, or be associated with, osteogenic materials such as demineralized bone particles or demineralized bone powder and medically/surgically useful substances as described above.

5 The implant can also be fabricated in whole or in part from a synthetic biocompatible, optionally bioabsorbable, ceramic or glass, or biocompatible metal. Examples include fibers of phosphate/silica glasses (bioglass), fibers of calcium phosphate, and metal fibers such as titanium or titanium nickel alloys (shape-memory metals).

10 In a particularly useful embodiment, the aforementioned material making up the implant can be wrapped with a monolithic piece, e.g., strips or sheets, fabricated from a suitable material that is remodeled by the body and replaced over time with new bone tissue. For example, the material can be wrapped or surrounded with demineralized bone strips cut from sheets which are composed of elongated bone
15 particles, commercially known as GRAFTON® Flex (Osteotech, Eatontown, NJ) as described, e.g., in aforementioned U.S. Patent 5,507,813.

 These demineralized bone strips can be affixed to the biocompatible osteogenic material by any convenient method, e.g., adhering the strips to the material utilizing adhesives, suturing the strips to the biocompatible osteogenic material,
20 braiding the strips around the biocompatible osteogenic material, etc.

 The implants of this invention can be utilized in a wide variety of orthopedic, neurosurgical and oral and maxillofacial surgical procedures such as the repair of simple and compound fractures and non-unions, external and internal fixations, joint reconstructions such as arthrodesis, general arthroplasty, cup arthroplasty of the hip,
25 femoral and humeral head replacement, femoral head surface replacement and total

joint replacement, repairs of the vertebral column including spinal fusion and internal fixation, tumor surgery, e.g. deficit filling, discectomy, laminectomy, excision of spinal cord tumors, anterior cervical and thoracic operations, repair of spinal injuries, scoliosis, lordosis and kyphosis treatments, intermaxillary fixation of fractures, mentoplasty, temporomandibular joint replacement, alveolar ridge augmentation and reconstruction, inlay bone grafts, implant placement and revision, sinus lifts, repair of ligaments or tendons in the hand, elbow, knee, foot, ankle or any other anatomical location, etc. These materials can be sutured or stapled in place for anchoring purposes and serve in guided tissue regeneration or as barrier materials.

10 It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore, the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the disclosure herein.

WHAT IS CLAIMED IS:

1 1. An implant comprising a quantity of flexible, elongated elements at
2 least some of which possess connective tissue-healing activity, the elements being
3 arranged in substantially common alignment along their longitudinal axis

1 2. The implant of Claim 1 wherein elongated elements are filaments,
2 threads, fibers or strips of biocompatible material possessing inherent or added
3 connective tissue-healing activity.

1 3. The implant of Claim 1 wherein elongated elements possess
2 connective tissue-healing activity which is one or more of chondrogenesis,
3 osteinduction, osteogenesis and osteoconduction.

1 4. The implant of Claim 2 wherein the biocompatible material is a tissue
2 selected from the group consisting of bone, ligament, tendon and small intestine
3 submucosa.

1 5. The implant of Claim 4 wherein the bone tissue is cortical bone, the
2 elongated elements of the bone being partially, superficially, segmentally or fully
3 demineralized.

1 6. The implant of Claim 2 wherein the biocompatible material contains at
2 least one added osteoinductive substance.

1 7. The implant of Claim 6 wherein the osteoinductive substance is
2 selected from the group consisting of bone-derived growth factor, bone morphogenic
3 proteins, osteogenic proteins, hormones, growth hormone, platelet derived growth
4 factor, insulin-like growth factors, DNA-encoding therapeutic agents, demineralized
5 bone, ceramic powders and bioglasses.

1 8. The implant of Claim 1 wherein elongated elements are bonded to each
2 other through chemical linkages.

1 9. The implant of Claim 1 wherein elongated elements range from about
2 1 cm to about 1 meter in length, from about 2 mm to about 30 mm in thickness and
3 from about 2 mm to about 30 mm in width.

1 10. The implant of Claim 1 wherein elongated elements range from about
2 3 cm to about 8 cm in length, about 0.5mm to about 10 mm in thickness and from
3 about 0.5 mm to about 10 mm in width.

1 11. The implant of Claim 4 wherein the bone tissue is cortical bone and the
2 elongated bone elements obtained therefrom possess a median length of from about 2
3 to about 200 mm, a median thickness of from about 0.05 to about 2 mm, a median
4 width of from about 1 mm to about 20 mm, a median length to median thickness ratio
5 of from about 50:1 to about 500:1 and a median length to median width ratio of from
6 about 10:1 to about 200:1.

1 12. The implant of Claim 4 wherein the bone tissue is cortical bone and the
2 elongated bone elements obtained therefrom possess a median length of from about
3 10 to about 100 mm, a median thickness of from about 0.2 to about 1 mm, a median
4 width of from about 2 to about 5 mm, a median length to median thickness ratio of
5 from about 50:1 to about 100:1 and a median length to median width ratio of from
6 about 50:1 to about 100:1.

1 13. The implant of Claim 1 wherein elongated elements in the form of
2 threads are assembled into yarns and the yarns are assembled into a braid.

1 14. The implant of Claim 1 wherein elongated elements in the form of
2 strips are assembled into a braid.

1 15. The implant of Claim 1 wherein elongated elements are twisted into a
2 cable.

1 16. The implant of Claim 1 wherein at least a portion of the elongated
2 elements are formed of a synthetic polymer, ceramic, glass or metal.

1 17. The implant of Claim 16 wherein the polymer, ceramic or glass is
2 bioresorbable.

1 18. The implant of Claim 1 wherein elongated elements are derived from
2 bone and other elongated elements are formed of at least one of synthetic polymer,
3 ceramic, glass or metal.

1 19. The implant of Claim 18 wherein the polymer, ceramic or glass is
2 bioresorbable.

1 20. The implant of Claim 18 wherein the elongated elements are
2 assembled into a braid.

1 21. The implant of Claim 19 wherein the elongated elements are
2 assembled into a braid.

1 22. The implant of Claim 1 containing at least one medically/surgically
2 useful substance that promotes or accelerates healing.

1 23. The implant of Claim 22 wherein the medically/surgically useful
2 substance is selected from the group consisting of collagen, insoluble collagen
3 derivatives, collagen lattices, antiviral agents, antimicrobials, antibiotics,
4 biocidal/biostatic sugars, amino acids, peptides, vitamins, inorganic elements, co-
5 factors for protein synthesis, hormones, endocrine tissue, endocrine tissue fragments,
6 synthesizers, enzymes, polymer cell scaffolds with parenchymal cells, angiogenic
7 drugs, antigenic agents, cytoskeletal agents, cartilage fragments, living cells, natural
8 extracts, genetically engineered or modified living cells, tissue transplants,
9 demineralized bone powder, DNA delivered by plasmid or viral vectors, autogenous
10 tissues, bioadhesives, bone morphogenic proteins, osteoinductive factor, fibronectin,
11 transforming growth factor-beta, endothelial cell growth factor, cementum attachment
12 extracts, ketaserin, insulin-like growth factor, platelet derived growth factors,

- 13 epidermal growth factor, interleukin, human alphathrombin, fibroblast growth factors,
14 periodontal ligament chemotactic factor, human growth hormone, animal growth
15 hormone, growth somatotropin, bone digesters, antitumor agents, immuno-
16 suppressants, permeation enhancers and nucleic acid.

- 1 24. The implant of Claim 4 wherein part or all of the demineralized bone
2 exhibits reduced osteoinductive properties.

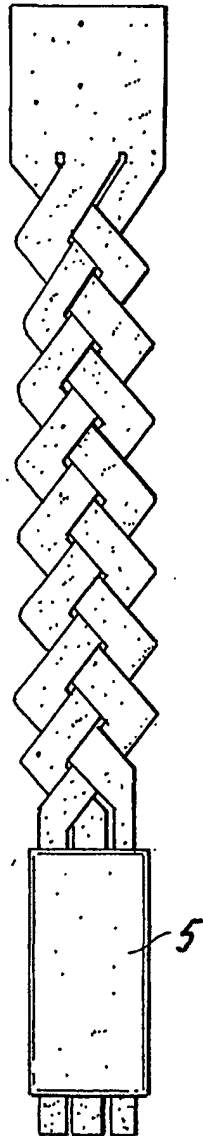


Fig. 1a

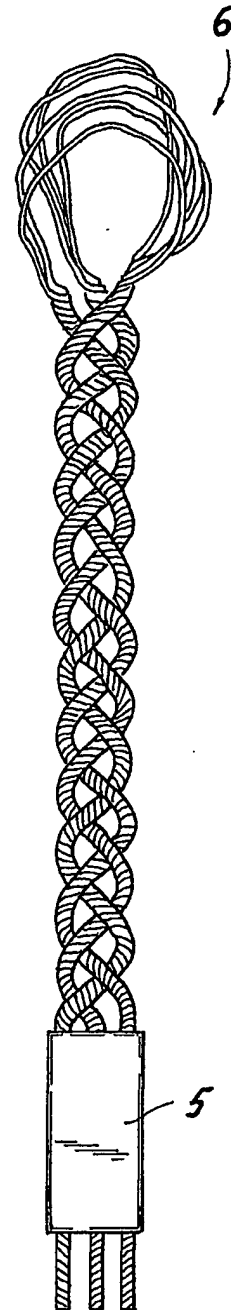


Fig. 1b

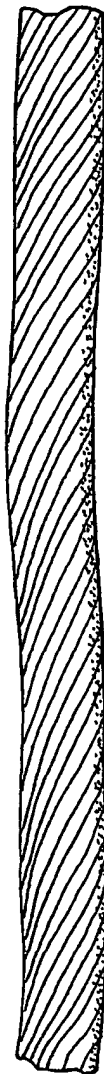


Fig. 1c Fig. 1d Fig. 1e

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

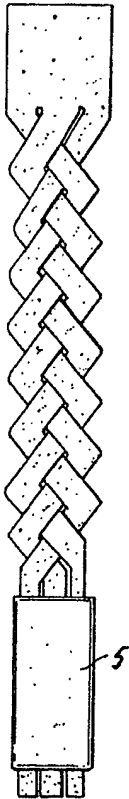
(10) International Publication Number
WO 02/056800 A3

- (51) International Patent Classification⁷: **A61F 2/08, 2/28**
- (21) International Application Number: **PCT/US01/47644**
- (22) International Filing Date: 7 December 2001 (07.12.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/254,378 8 December 2000 (08.12.2000) US
- (71) Applicant (for all designated States except US): **OS-TEOTECH, INC.** [US/US]; 51 James Way, Eatontown, NJ 07724 (US).
- (71) Applicants and
- (72) Inventors: **BOYCE, Todd, M.** [US/US]; 515 Wellington Place, Aberdeen, NJ 07747 (US). **SHIMP, Lawrence, A.** [US/US]; 313 Route 79, Morganville, NJ 07751 (US).
- (74) Agents: **DILWORTH, Peter, G.** et al.; Dilworth & Barrese, LLP, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: **IMPLANT FOR ORTHOPEDIC APPLICATIONS**

(57) Abstract: An implant for orthopedic applications includes a quantity of flexible, elongated elements at least some of which possess connective tissue-healing activity, the elongated elements being arranged in substantially common alignment along their longitudinal axis.



WO 02/056800 A3



Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:

20 March 2003

INTERNATIONAL SEARCH REPORT

national Application No
RU/US 01/47644

| A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61F2/08 A61F2/28 | | |
|---|--|--|
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61F | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | US 6 123 731 A (BOYCE TODD M ET AL) 26 September 2000 (2000-09-26) cited in the application column 4, line 2 -column 5, line 43; claims 13,14 | 1-8, 16-19, 22-24 |
| X | US 5 092 887 A (GENDLER EL) 3 March 1992 (1992-03-03) cited in the application column 4, line 46 - line 57 column 6, line 54 -column 7, line 8 | 1-5,9,10 |
| Y | US 5 507 813 A (DOWD MICHAEL ET AL) 16 April 1996 (1996-04-16) cited in the application column 2, line 63 -column 3, line 22 column 4, line 26 - line 57 | 11,12 |
| Y | | 11,12 |
| A | | 2-5,7, 22-24 |
| | -/-- | |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. | | |
| * Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the International filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the International filing date but later than the priority date claimed *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family | | |
| Date of the actual completion of the international search | | Date of mailing of the International search report |
| 2 September 2002 | | 10/09/2002 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | | Authorized officer Wolf, C |

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 01/47644

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|--------------------------------|
| X | EP 0 306 018 A (BIO PRODUCTS INC) 8 March 1989 (1989-03-08) abstract; figures 1,1A page 5, line 3 - line 11 page 5, line 51 - line 56 ----- | 1-4,6-8, 13,14, 22,23 |
| X A | US 5 263 984 A (LI SHU-TUNG ET AL) 23 November 1993 (1993-11-23) cited in the application abstract; figures 24-D column 6, line 9 - line 28 column 8, line 46 - line 68 ----- | 1-4,8, 13-15 9,20,21 |
| X | EP 0 485 986 A (UNITED STATES SURGICAL CORP) 20 May 1992 (1992-05-20) abstract; figures 1-3 page 10, line 17 - line 29; example 3 ----- | 1-3,6,7, 13-17 |
| X | US 5 378 469 A (KEMP PAUL D ET AL) 3 January 1995 (1995-01-03) cited in the application column 3, line 5 - line 7 column 5, line 24 - line 29 column 6, line 39 - line 53 ----- | 1-4,8, 13-15 |
| A | US 5 711 960 A (SHIKINAMI YASUO) 27 January 1998 (1998-01-27) cited in the application column 5, line 8 - line 25 column 10, line 6 - line 19 column 10, line 50 - line 61 column 13, line 49 -column 14, line 40 ----- | 1-3,6,7, 13,14, 16-18 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/47644

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|--|--|
| US 6123731 A | 26-09-2000 | AU 2588699 A BR 9907670 A CA 2320481 A1 CN 1290182 T EP 1053032 A1 HU 0102991 A2 JP 2002502637 T NO 20003961 A NZ 506577 A PL 342266 A1 WO 9939757 A1 US 6294041 B1 | 23-08-1999 18-12-2001 12-08-1999 04-04-2001 22-11-2000 28-11-2001 29-01-2002 03-10-2000 31-05-2002 04-06-2001 12-08-1999 25-09-2001 |
| US 5092887 A | 03-03-1992 | NONE | |
| US 5507813 A | 16-04-1996 | AT 213958 T CA 2177017 A1 DE 69430069 D1 EP 0732947 A1 JP 9506281 T WO 9515776 A1 | 15-03-2002 15-06-1995 11-04-2002 25-09-1996 24-06-1997 15-06-1995 |
| EP 0306018 A | 08-03-1989 | EP 0306018 A1 US 5078744 A | 08-03-1989 07-01-1992 |
| US 5263984 A | 23-11-1993 | US 4880429 A US 5007934 A US 5116374 A AU 676832 B2 AU 4048493 A CA 2134111 A1 DE 69332079 D1 EP 0639959 A1 JP 7505326 T WO 9321857 A2 AT 87452 T AU 605723 B2 AU 2424588 A DE 3879921 D1 DE 3879921 T2 EP 0324852 A1 JP 2500654 T JP 2754027 B2 US 6042610 A WO 8900413 A1 US 5624463 A US 5681353 A US 5735903 A US 5735902 A US 5158574 A US 5306311 A US 5258043 A AT 125441 T AU 637605 B2 AU 5337990 A CA 2050471 A1 DE 69021204 D1 DE 69021204 T2 | 14-11-1989 16-04-1991 26-05-1992 27-03-1997 29-11-1993 11-11-1993 08-08-2002 01-03-1995 15-06-1995 11-11-1993 15-04-1993 17-01-1991 13-02-1989 06-05-1993 14-10-1993 26-07-1989 08-03-1990 20-05-1998 28-03-2000 26-01-1989 29-04-1997 28-10-1997 07-04-1998 07-04-1998 27-10-1992 26-04-1994 02-11-1993 15-08-1995 03-06-1993 26-09-1990 03-09-1990 31-08-1995 07-12-1995 |

INTERNATIONAL SEARCH REPORT
information on patent family members

International Application No
PCT/US 01/47644

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| US 5263984 A | | EP 0461201 A1 | 18-12-1991 |
| | | ES 2077676 T3 | 01-12-1995 |
| | | JP 4504968 T | 03-09-1992 |
| | | JP 3100156 B2 | 16-10-2000 |
| | | WO 9009769 A1 | 07-09-1990 |
| | | US 5108438 A | 28-04-1992 |
| EP 0485986 A | 20-05-1992 | US 5217495 A | 08-06-1993 |
| | | EP 0485986 A1 | 20-05-1992 |
| | | US 5376118 A | 27-12-1994 |
| US 5378469 A | 03-01-1995 | US 5256418 A | 26-10-1993 |
| | | AT 180158 T | 15-06-1999 |
| | | CA 2120736 A1 | 15-04-1993 |
| | | DE 69229232 D1 | 24-06-1999 |
| | | DE 69229232 T2 | 09-12-1999 |
| | | DK 607346 T3 | 08-11-1999 |
| | | EP 0607346 A1 | 27-07-1994 |
| | | ES 2132132 T3 | 16-08-1999 |
| | | GR 3030797 T3 | 30-11-1999 |
| | | JP 7500037 T | 05-01-1995 |
| | | WO 9306791 A1 | 15-04-1993 |
| | | AT 141171 T | 15-08-1996 |
| | | CA 2039910 A1 | 07-10-1991 |
| | | DE 69121301 D1 | 19-09-1996 |
| | | DE 69121301 T2 | 02-01-1997 |
| | | DK 457430 T3 | 23-12-1996 |
| | | EP 0457430 A2 | 21-11-1991 |
| | | ES 2093077 T3 | 16-12-1996 |
| | | GR 3021312 T3 | 31-01-1997 |
| | | JP 3221690 B2 | 22-10-2001 |
| | | JP 4227264 A | 17-08-1992 |
| US 5711960 A | 27-01-1998 | WO 9609099 A1 | 28-03-1996 |
| | | DE 69426414 D1 | 18-01-2001 |
| | | DE 69426414 T2 | 03-05-2001 |
| | | EP 0677297 A1 | 18-10-1995 |
| | | FI 952515 A | 11-07-1995 |
| | | WO 9508354 A1 | 30-03-1995 |
| | | JP 3243679 B2 | 07-01-2002 |
| | | JP 7148243 A | 13-06-1995 |
| | | EP 0785005 A1 | 23-07-1997 |
| | | US 5913399 A | 22-06-1999 |